

An Appendix of Pending Claims containing Claims 12-25 which are under consideration is attached hereto for the Examiner's convenience.

**Rejection Under 35 U.S.C. § 101: Lack of Asserted utility**

Claims 12-25 are rejected under 35 U.S.C. § 101 for lack of specific asserted or a well established utility. Applicants respectfully traverse.

The Examiner suggests that the synthesis of nucleic acids utilizing such nucleosides comprising bulky adducts like ETMs (electron transfer moiety) are not enabled given the presumption that bulky adducts may hinder enzymatic or chemical synthesis of nucleic acids. The Examiner also contends that the specification (1) fails to teach the claimed "nucleoside comprising a covalently attached electron transfer moieties" and (2) fails to disclose an asserted specific and substantial utility for the nucleoside. Thus, the Examiner concludes that the claims are inoperative and fail to meet the utility requirement under 35 U.S.C. 101. Applicants respectfully disagree.

Applicants assert that the synthesis of nucleic acids utilizing nucleosides comprising bulky adducts like ETMs (electron transfer moiety), as taught in the current invention, does not hinder enzymatic or chemical synthesis of nucleic acids. As a preliminary matter, Applicants assert that the specification provides adequate support for making and using ETM-labeled nucleosides/nucleotides; for example: see page 20, line 7 through page 25, line 10 and all examples from page 37, line 21 through page 44, line 2. These pages outline both standard solid phase phosphoramidite synthesis as well as enzymatic synthesis, using, for example, Taq 1 polymerase. The specification also describes various utilities for nucleic acids with ETMs; for example, see page 6, lines 20-23 which describes use of such nucleic acids as non-

radioactive DNA markers, diagnostic probes, or novel bioconductors. Further in support of utility and enablement, Applicants hereby present two articles: (1) A chapter published in a commercially available Handbook by Molecular Probes, namely: "Chemically modified nucleotides, oligonucleotides and nucleic acids": Chapter 8-Section 8.2 in the 'Handbook of Fluorescent probes and Research chemicals' by Richard P. Haugland, 6th edition (attached hereto as Exhibit A); and (2) a research article by Hurley, D. and Tor, Y., *J. Am. Chem. Soc.*, (1998) 120, 2194-5 (attached hereto as Exhibit B). Exhibit A describes fluorophore labeled (bulky adducts; see Fig. 8.4 and Table 8.2) nucleosides and oligonucleotides, that is, Chromatide nucleotides, for enzymatic incorporation into nucleic acids (see page 157, column 1, line 18-21). Furthermore, preliminary experiments were performed to show that the Chromatide nucleotides were functional with a variety of nucleic acid modifying enzymes: viz; Taq polymerase, DNA polymerase, Klenow polymerase, TdT transferase, SP6, T3 and T7 RNA polymerase (see column 1, last paragraph through page 158, first paragraph). Exhibit B describes the synthesis of metal-containing phosphoramidites during solid-phase oligonucleotide synthesis (see Scheme 1 and column 1, line 15-21). Thus, there is prior art that teaches the incorporation of bulky adducts during nucleic acid synthesis both using solid-phase standard phosphoramidite chemistry as well as enzymatic synthesis. Since the current specification must be read in view of the existing art, the Examiner's presumption that "incorporation of nucleosides comprising bulky adducts like ETMs into nucleic acids using enzymatic synthesis would not be expected by one of skill in the art" is incorrect.

Since, Applicants have asserted a well established utility for their invention, Applicants respectfully request withdrawal of the rejection of Claims 12-25 under 35 U.S.C. § 101.

**Rejection Under 35 U.S.C. § 112, first paragraph: Lack of enablement**

Claims 12-25 are rejected under 35 U.S.C. § 112, first paragraph for a lack of enablement based on the finding that the claims are not supported by a specific asserted utility or a well-established utility. Applicants respectfully traverse.

In view of the discussions above, Applicants have asserted a specific and substantial utility for their invention with adequate support in the specification and in exhibits attached hereto. Thus, one skilled in the art is fully enabled to make and use this invention.

Accordingly, Applicants respectfully request withdrawal of the rejections to Claims 12-25 under 35 U.S.C. 112, first paragraph for lack of enablement.

**Rejection Under 35 U.S.C. 112, first paragraph: Lack of written description**

Claims 12-25 are rejected under 35 U.S.C. 112, first paragraph for lack of written description of subject matter to reasonably convey to persons skilled in the art that applicant had possession of the claimed invention at the time of filing of the application. Specifically, the Examiner contends that the specification fails to describe "nucleoside (or nucleotide) comprising a covalently attached transfer moiety" as a molecule distinct from a nucleic acid. Applicants respectfully traverse.

Again, in view of the current amendments and in light of the discussions above, Applicants submit that the specification, as filed, fully complies with the written description requirement. That is, Applicants have fully provided written description of how to make and use ETM-labeled nucleosides/nucleotides in nucleic acids, for example: see page 20, line 7 through page 25, line 10 and all examples from page 37, line 21 through page 44, line 2.

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Hence, Applicants respectfully request withdrawal of the rejection of claims 12-25 under 35 U.S.C. 112, first paragraph for lack of written description.

**Conclusion**

Applicants respectfully submit that the claims are now in condition for allowance and early notification to that effect is respectfully requested. If the Examiner feels there are further unresolved issues, he/she is requested to phone the undersigned at (415)-781-1989.

Respectfully submitted,

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#### **APPENDIX OF PENDING CLAIMS**

12. A nucleoside comprising a ribose comprising a covalently attached electron transfer moiety at the 2' position.
13. A nucleoside according to claim 12 wherein said electron transfer moiety is an organic electron transfer moiety.
14. A nucleoside according to claim 12 wherein said electron transfer moiety is a transition metal complex.
15. A nucleoside according to claim 12 wherein said transition metal complex comprises ruthenium.
16. A nucleoside according to claim 12 wherein said transition metal complex comprises iron.
17. A nucleoside according to claim 12 wherein said transition metal complex comprises osmium.
18. A nucleoside according to claim 12 wherein said transition metal complex comprises rhenium.
19. A nucleoside according to claim 12 wherein said transition metal complex comprises cobalt.
20. A nucleoside according to claim 12 wherein said transition metal complex comprises palladium.
21. A nucleoside according to claim 12 wherein said transition metal complex comprises platinum.
22. A nucleoside according to claim 12 wherein said electron transfer moiety is attached via an amine group at said 2' position.
23. A nucleoside according to claim 12 wherein said electron transfer moiety is attached via a linker at said 2' position.
24. A nucleotide comprising a ribose comprising a covalently attached electron transfer moiety at the 2' position.
25. A nucleic acid comprising a nucleoside comprising a ribose comprising a covalently attached electron transfer moiety at the 2' position.